

Coronary Vasodilator Reserve: A Clue to the Explanation of ^{201}Tl Redistribution Patterns Early After Successful Primary Stenting for Acute Myocardial Infarction

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OBJECTIVES	We sought to assess the mechanism and significance of different ^{201}Tl redistribution patterns after successful primary stenting following acute myocardial infarction (AMI).
BACKGROUND	The mechanism of ^{201}Tl reverse redistribution and the impact of different redistribution patterns on the recovery of contractility after successful reperfusion therapy for AMI remain unclear.
METHODS	We studied 41 consecutive patients with successful primary stenting for a first AMI. Patients underwent predischARGE and six-month follow-up dipyridamole stress-reinjection single photon emission tomography (SPECT), coronary and left ventricular angiography. Intracoronary Doppler assessment of coronary flow reserve (CFR) was performed before discharge.
RESULTS	Four patient groups were identified according to predischARGE SPECT: patients with I: nonreversible defects ($n = 8$), II: redistribution ($n = 7$), III: reverse redistribution ($n = 21$), IV: no defect ($n = 5$). At follow-up contractility recovery increased in a stepwise fashion from groups I to IV ($19 \pm 41\%$, $40 \pm 53\%$, $70 \pm 28\%$, $78 \pm 33\%$, $p = 0.01$). Compared with patients with redistribution, those with reverse redistribution had lower infarct-related artery (IRA) CFR (2.2 ± 0.5 vs. 2.8 ± 0.9 , $p = 0.03$) but higher contractility recovery.
CONCLUSIONS	Variable ^{201}Tl redistribution patterns, early after successful stenting for AMI, may predict different degrees of late contractility recovery. The lower IRA CFR and the higher contractility recovery in areas with reverse redistribution suggest more severe microvascular dysfunction and less severe myocardial injury in such areas compared with those with redistribution. (J Am Coll Cardiol 2002;40:877–81) © 2002 by the American College of Cardiology Foundation

Percutaneous transluminal coronary angioplasty with systematic stenting is considered as the gold standard for primary treatment after acute myocardial infarction (AMI), combining advantages of conventional balloon angioplasty over thrombolytic therapy (1,2), with lower restenosis rates (3,4). However, clinical outcome and recovery of myocardial contractility after successful reperfusion therapy are influenced by the extent of microvascular damage and the persistence of viable myocardium (5–7).

^{201}Tl single photon emission computed tomography (SPECT) is commonly used to detect myocardial viability after AMI. ^{201}Tl redistribution and reverse redistribution, at rest or under stress protocols, have been reported to detect myocardial viability (8–12). However, the mechanism of reverse redistribution and the impact of different patterns on late contractility recovery remain unclear. We sought to assess the hypothesis that different redistribution patterns early after successful primary stenting for AMI may predict different outcomes of contractility recovery and reflect different degrees of coronary vasodilator reserve.

METHODS

Study protocol. The study included 41 patients, successfully treated by primary stenting after their first AMI within 6 h from the onset of the symptoms. Patients with cardiogenic shock, left main or multivessel disease, diffusely diseased (>1 stenosis) infarct-related artery (IRA), and distal coronary occlusion were excluded. Single photon emission computed tomography was performed 6 to 10 days after the AMI. Coronary angiography and left ventriculography were performed within 24 h of SPECT in all patients. Both tests were also scheduled for the six-month follow-up. Intracoronary Doppler assessment of coronary flow reserve (CFR) was performed during the predischARGE catheterization. All patients gave informed consent, and the study was approved by our local ethics committee.

Angiography and stenting. Before the procedure all patients received heparin (100 IU/kg) and aspirin (500 mg) intravenously. Coronary angiography and stenting were performed with standard techniques. After the stenting all patients received ≥ 72 h heparin infusion, ticlopidine (500 mg/day), and aspirin (100 mg/day) for 30 days, followed by aspirin (250 mg/day) alone.

Left ventricular ejection fraction (EF) was quantified, in the 30° right anterior oblique projection. Regional contractility was assessed in 20 segments using Slager's method

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Manuscript received December 28, 2001; revised manuscript received April 22, 2002, accepted May 24, 2002.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
CFR	= coronary flow reserve
EF	= ejection fraction
IRA	= infarct-related artery
SPECT	= single photon emission computed tomography

(13,14). Segments were considered as hypokinetic when <2 SD below the mean of the corresponding segments of a reference population (30 patients with chest pain and normal angiography). The difference in the number of hypokinetic segments between predischARGE and follow-up and its ratio on the predischARGE number of hypokinetic segments (recovery index) were used to study late contractility recovery.

201Tl SPECT. Single photon emission computed tomography was performed using a standard dipyridamole stress-reinjection protocol (15,16). A 4.5 MBq \times body mass index dose of 201Tl was injected after intravenous infusion of dipyridamole and 1.5 MBq \times body mass index 4 h later. Image acquisition was performed after each injection using an APEX SPX-4 HR (Elsint, Haifa, Israel) gamma camera. Stress and reinjection images were analyzed using two-dimensional polar maps each adjusted for its own maximal value. The size of the defect was calculated using the 55% threshold of maximal uptake (17) and expressed as a percentage of the left ventricle. A relative increase or decrease in the defect size of at least 10% (twice the variability of measurements in our center) between stress and reinjection images was considered significant (11,12). Four patient groups were identified: I: nonreversible defects; II: redistribution (decrease of the defect size between stress and reinjection $>10\%$); III: reverse redistribution (increase of the defect size between stress and reinjection $>10\%$); IV: no defect at either stress or reinjection.

Intracoronary flow measurements. Absolute CFR was assessed in the IRA and a normal remote artery using a 0.014-in. Doppler-tipped flow wire (Cardiometrics Inc., Mountain View, California) (18). Relative CFR was defined by the ratio of IRA to remote artery CFR.

Statistical analysis. Continuous variables are presented as mean \pm SD. A paired *t* test and a chi-square test were used for the comparison of the means and qualitative variables. A one-way analysis of variance with a Fisher's protected least significant difference test was used to compare variables between patient groups. A *p* < 0.05 was considered statistically significant.

RESULTS

Patient population. The baseline characteristics were comparable between the four patient groups with the exception of a lower baseline ST-segment elevation in group II compared with groups I and IV (*p* < 0.05) and a higher preangioplasty Thrombolysis in MI (TIMI) grade in group IV compared with group II (*p* < 0.05) (Table 1). Clinical follow-up was completed in all patients. Follow-up SPECT and angiography were performed in 37 patients (90%) 6 \pm 1 months after the AMI. At follow-up no death or AMI had occurred, and target vessel revascularization was performed in 11 patients (26.8%) after the follow-up SPECT and angiography.

Angiographic and SPECT data. Compared with predischARGE, left ventricular EF and hypokinetic segments regional EF increased at follow-up (60 \pm 11% vs. 63 \pm 10%, *p* = 0.02 and 1.4 \pm 0.8% vs. 5.1 \pm 6.9%, *p* < 0.01 , respectively). At follow-up all IRAs were patent, and angiographic in-stent restenosis (diameter stenosis $>50\%$) was found in 10 patients (27%). Among patients with restenosis, seven had reversible 201Tl stress defects at follow-up, but none had reverse redistribution. The global and regional EF, the number of hypokinetic segments, the

Table 1. Baseline Characteristics

	Group I (n = 8)	Group II (n = 7)	Group III (n = 21)	Group IV (n = 5)
Age (yrs)	57 \pm 8	53 \pm 7	58 \pm 10	54 \pm 4
Men	7 (88%)	6 (86%)	17 (81%)	3 (60%)
Hypercholesterolemia	4 (50%)	3 (43%)	8 (38%)	2 (40%)
Systemic hypertension	3 (38%)	1 (14%)	4 (19%)	1 (20%)
Diabetes mellitus	0	0	3 (14%)	0
Current smokers	4 (50%)	6 (86%)	14 (67%)	2 (40%)
Infarct location				
Anterior	4 (50%)	2 (71%)	8 (62%)	2 (60%)
Inferior	4 (50%)	5 (29%)	13 (38%)	3 (40%)
Symptom to reperfusion time (min)	209 \pm 102	253 \pm 129	207 \pm 88	178 \pm 19
ST-segment elevation (mm)				
Baseline	3.9 \pm 1	2.5 \pm 0.7*	3.4 \pm 1.2	4.1 \pm 2
After stenting	1.6 \pm 1.5	0.6 \pm 1.1	1.1 \pm 1.2	0.5 \pm 0.5
Prereperfusion				
TIMI flow grade	0.3 \pm 0.5	0.1 \pm 0.4	0.3 \pm 0.7	1 \pm 1†
Collateral flow grade	0.9 \pm 1	1.4 \pm 1	1.4 \pm 1.2	2 \pm 1.2

**p* < 0.05 , group II vs. groups I and IV; †*p* < 0.05 , group IV vs. group II.
TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Patients With Redistribution Compared With Those With Reverse Redistribution

	Group I (n = 8)	Group II (n = 7)	Group III (n = 21)	Group IV (n = 5)	Global p Value
Peak creatine kinase (IU/l)	4,390 ± 2,452	2,241 ± 2,452	1,945 ± 1,848	1,718 ± 1,284	0.03
In-hospital defect size (%)					
Stress	38 ± 14	22 ± 22	12 ± 14	0	0.0002
Rest	39 ± 14	17 ± 19	18 ± 16	0	0.0009
Follow-up defect size (%)					
Stress	33 ± 20	15 ± 15	15 ± 17	9 ± 12	0.07
Rest	31 ± 20	11 ± 15	10 ± 16	0	0.01
Infarct artery flow reserve	2 ± 0.6	2.8 ± 0.9	2.2 ± 0.5*	2.1 ± 0.4	0.049
In-hospital left ventricular					
EDV (ml/m ²)	70 ± 22	83 ± 12	68 ± 19	53 ± 6	0.047
ESV (ml/m ²)	33 ± 15	36 ± 9	25 ± 11*	20 ± 5	0.03
EF (%)	53 ± 13	57 ± 6	63 ± 11	62 ± 5	0.09
Hypokinetic segments					
n	6.1 ± 4.2	4.6 ± 3.9	4.7 ± 3.4	2.8 ± 1.1	0.4
Regional EF (%)	1.2 ± 0.7	1.2 ± 0.6	1.7 ± 1.2	1.4 ± 0.7	0.7
Follow-up left ventricular					
EDV (ml/m ²)	78 ± 16	77 ± 20	68 ± 16	71 ± 12	0.5
ESV (ml/m ²)	36 ± 15	31 ± 12	23 ± 10	25 ± 6	0.07
EF (%)	55 ± 11	61 ± 8	66 ± 10	64 ± 4	0.06
Hypokinetic segments					
n	5.6 ± 4.1	3.3 ± 3.1	2.1 ± 2.1	0.8 ± 1.3	0.02
Regional EF (%)	1.6 ± 1.1	2.5 ± 2.4	8.1 ± 8.9	4.7 ± 4.3	0.2
Hypokinetic segments					
Δ n	0.6 ± 1.9	1.3 ± 1.7	3.1 ± 2.1*	2 ± 1	0.03
Δ Regional EF (%)	0.6 ± 0.9	1.5 ± 2.1	6.6 ± 9.2	3.8 ± 5.1	0.3
Recovery index (%)	19 ± 41	40 ± 53	70 ± 28	78 ± 33	0.01

*p < 0.05 between groups II and III.

EDV = end diastolic volume; ESV = end systolic volume; EF = ejection fraction; Δ = difference between predischage and follow-up.

recovery index, and the stress and rest defect sizes were comparable between patients with and those without restenosis.

Compared with the predischage SPECT, at follow-up there were more patients with redistribution (16 vs. 7, p = 0.001) and less patients with reverse redistribution (2 vs. 21, p < 0.0001). This resulted in a smaller rest defect size (p = 0.002) at follow-up compared with predischage, while the stress defect size did not significantly change.

In patients with reverse redistribution, the follow-up infarct size (10 ± 16%) was more accurately predicted at predischage by the stress defect size (12 ± 14%, p = NS) than the reinjection defect size (18 ± 16%, p = 0.002). This difference was not observed in the other groups.

Comparison of different patient groups. At follow-up restenosis rate was comparable between different groups (25%, 14%, 29%, 20% in groups I to IV, respectively) (Table 2).

Compared with other patients, those with a nonreversible defect had more extensive necrosis and lower left ventricular EF at predischage and follow-up. There was a stepwise increase (p = 0.01) of the recovery index from group I towards group IV (Fig. 1).

Compared with patients with redistribution, those with reverse redistribution had a comparable infarct size as revealed by peak creatine kinase values and ²⁰¹Tl defect size, lower CFR in the IRA (p = 0.02), and lower left ventricular

end-diastolic (p = 0.06) and end-systolic (p = 0.03) volume indexes. There was also a trend towards a lower relative CFR in group III compared with group II (0.84 ± 0.15 vs. 0.95 ± 0.15, p = 0.1). The reduction in the number of hypokinetic segments between in-hospital and follow-up ventriculography was also significantly higher in patients with reverse redistribution (p = 0.04) with a trend towards a higher recovery index (p = 0.07).

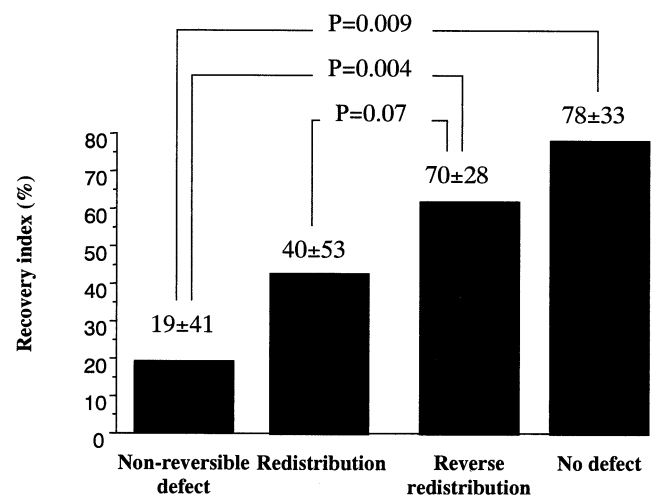


Figure 1. Late contractility recovery in different patient groups.

DISCUSSION

While the relation between myocardial viability detected by ^{201}Tl SPECT and the recovery of contractility is widely established (8,16,17,19), our study is the first to show a possible grading of viability according to the predischARGE redistribution patterns of dipyridamole stress SPECT. This grading is correlated to the magnitude of the late contractility recovery.

^{201}Tl redistribution patterns. In normally perfused or reperfused myocardium, ^{201}Tl kinetics follow three phases of influx and efflux: very early vascular, early interstitial, and late cellular phases (20–22).

A normal ^{201}Tl pattern needs the integrity of the three phases of ^{201}Tl kinetics. Such conditions are probably present in patients with no defect after reperfusion (group IV). In such patients the persistence of a certain degree of anterograde flow, as shown by the higher prereperfusion TIMI grade in this study, might protect both the microvasculature and the myocardium.

On the other extreme, it is well established that, after myocardial infarction, totally necrotic regions show absence of ^{201}Tl uptake (23). Such situation generates nonreversible ^{201}Tl defect as seen in group I.

In regions with ischemic insult followed by reperfusion, such as perinecrotic areas, ^{201}Tl uptake is delayed as a consequence of retarded cellular influx (24), accelerated efflux (25), and increased late cellular recapture of ^{201}Tl “trapped” in distally occluded microvasculature (26). On the other hand, it is established that an increase in the coronary artery flow, above the physiologic range, reduces the ^{201}Tl extraction (27). The association of a preserved coronary vasodilator reserve (high CFR), the dipyridamole-induced overflow, and the delayed ^{201}Tl uptake in such areas may explain the reduced stress uptake and the redistribution pattern seen in group II.

The reverse redistribution pattern has been described in different clinical situations and in association with different types of stress or rest redistribution protocols (9–12,28). Several mechanisms of this phenomenon have been proposed, but they all remain more or less speculative.

One possible explanation of reverse redistribution pattern is the relative nature of perfusion information provided by ^{201}Tl SPECT. Reverse redistribution could be visualized in regions supplied by nonstenosed coronary arteries, with normal ^{201}Tl kinetics, in contrast with those with late uptake or slow washout such as areas of hibernating myocardium (11). These mechanisms are inapplicable to our data concerning patients with single-vessel disease and reverse redistribution in the infarct area. The previously reported background oversubtraction and spurious reverse redistribution (28) hypotheses are also excluded in our study by the absence of background subtraction and the uniform filtering during reconstruction.

A faster clearance of ^{201}Tl has also been reported as a possible explanation of reverse redistribution in ischemia-

reperfusion models. Several possible mechanisms of faster ^{201}Tl clearance have been described. First, it is established that the interstitial ^{201}Tl washout is faster than the cellular washout (20,22). The expansion of the interstitial tissue, due to interstitial edema or hemorrhage, could explain its visualization on SPECT stress images. Hence, the fast interstitial washout could explain the visualization of a defect, in absence of reinjection, at rest. Second, an accelerated ^{201}Tl cellular efflux reported after ischemic insult (29) could also explain the reverse redistribution pattern in the same way. Third, in regions supplied by critically stenosed arteries, a possible regulatory mechanism of collateral circulation may result in higher flow rates at rest compared with stress. This differential in flow may cause impairment of the ^{201}Tl myocardial retention and reverse redistribution (11).

This study is the first to assess reverse redistribution in a dipyridamole stress-reinjection protocol after successful reperfusion and angiographically normalized IRA. This protocol was used in our study for two major reasons. First, dipyridamole injection increases myocardial capillary flow in patent coronary arteries without stenosis. Its effects are comparable to those of adenosine used for the measurement of the CFR. Second, we hypothesized that if the faster ^{201}Tl clearance hypotheses were confirmed by our data, the ^{201}Tl reinjection would reduce the likelihood of visualizing reverse redistribution (11).

In our study the reverse redistribution pattern was found in 21 (51%) patients despite the ^{201}Tl reinjection. This pattern was associated with a reduced CFR in the corresponding artery, which, in absence of stenosis, is suggestive of microvascular dysfunction. It is conceivable that the flow increase induced by dipyridamole would increase ^{201}Tl uptake in areas with microvascular dysfunction masking the ^{201}Tl -uptake gradient between injured and normal areas. This gradient could become unmasked on reinjection images in such areas causing reverse redistribution. The gradual improvement of coronary vasodilator reserve reported during the months after a reperfused AMI (30) is concordant with the dramatic reduction of reverse redistribution patterns at follow-up compared with predischARGE images in our study.

Compared with regions with redistribution, those with reverse redistribution show less left ventricular remodeling and better contractility recovery, as if, paradoxically, the microvascular dysfunction would prevent deep myocardial injury. A possible explanation for this finding could be a more gradual myocardial reperfusion with reduced exposure of myocytes to reperfusion injury-generating agents such as free radicals.

Study limitations. These findings only apply to patients with single-vessel disease, early successful stenting for AMI, and reverse redistribution using a dipyridamole stress-reinjection protocol. Other mechanisms, alone or associated with the microvascular hypothesis, could not be excluded by our study.

The recovery index used in our study to assess regional contractility recovery reflects the amount of stunned myocardium regardless of the extension of the infarct, but its clinical relevance in a particular patient should be viewed with caution. The clinical implications of our study need to be confirmed by further studies.

Conclusions. ²⁰¹Tl redistribution patterns after dipyridamole stress, early after successful primary stenting for AMI, may predict variable degrees of late contractility recovery. Compared with the redistribution pattern, reverse redistribution is associated with lower CFR of the IRA, but less left ventricular remodeling and better contractility recovery. This finding is suggestive of a deeper myocardial functional injury in the former and a microvascular dysfunction in the latter. Our study also implies that the early assessment of infarct size should be done on stress images in patients with reverse redistribution.

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